DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE - dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine sulfate and amphetamine aspartate capsule, extended release

Global Pharmaceuticals, Division of Impax Laboratories Inc.

CII
Rx Only

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY. MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

DESCRIPTION

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules is a once daily extended-release, single-entity amphetamine product. Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d,l-amphetamine aspartate monohydrate. The Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules® capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine from Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules compared to the conventional ADDERALL® (immediate-release) tablet formulation.

EACH CAPSULE CONTAINS:	5 mg	10 mg	15 mg	20 mg	25 mg	30 mg
Dextroamphetamine Saccharate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Aspartate Monohydrate	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Dextroamphetamine Sulfate USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Amphetamine Sulfate USP	1.25 mg	2.5 mg	3.75 mg	5.0 mg	6.25 mg	7.5 mg
Total amphetamine base equivalence	3.1 mg	6.3 mg	9.4 mg	12.5 mg	15.6 mg	18.8 mg

Inactive Ingredients and Colors: The inactive ingredients in Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules capsules include: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, opadry beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5 mg, 10 mg, and 15 mg capsules also contain FD&C Blue #2. The 20 mg, 25 mg, and 30 mg capsules also contain red iron oxide and yellow iron oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

Pharmacokinetics

Pharmacokinetic studies of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules have been conducted in healthy adult and pediatric (6-12 yrs) subjects, and adolescent (13-17 yrs) and pediatric patients with ADHD. Both ADDERALL® (immediate-release) tablets and Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules contain d-amphetamine and l-amphetamine salts in the ratio of 3:1. Following administration of ADDERALL® (immediate-release), the peak plasma concentrations occurred in about 3 hours for both d-amphetamine and l-amphetamine.
The time to reach maximum plasma concentration (T_{max}) for Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules is about 7 hours, which is about 4 hours longer compared to ADDERALL® (immediate-release). This is consistent with the extended-release nature of the product.

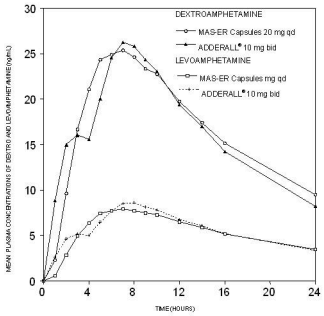

Figure 1 Mean d-amphetamine and l-amphetamine plasma concentrations following administration of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules (MAS-ER) **20 mg (8am) and ADDERALL® (immediate-release) 10 mg bid (8am and 12 noon) in the fed state.**

A single dose of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules 20 mg capsules provided comparable plasma concentration profiles of both d-amphetamine and l-amphetamine to ADDERALL® (immediate-release) 10 mg bid administered 4 hours apart.

The mean elimination half-life for d-amphetamine is 10 hours in adults; 11 hours in adolescents aged 13-17 years and weighing less than or equal to 75 kg/165 lbs; and 9 hours in children aged 6 to 12 years. For the l-amphetamine, the mean elimination half-life in adults is 13 hours; 13 to 14 hours in adolescents; and 11 hours in children aged 6 to 12 years. On a mg/kg body weight basis, children have a higher clearance than adolescents or adults (See Special Populations).

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules demonstrates linear pharmacokinetics over the dose range of 20 to 60 mg in adults and adolescents weighing greater than 75 kg/165lbs, over the dose range of 10 to 40 mg in adolescents weighing less than or equal to 75 kg/165 lbs, and 5 to 30 mg in children aged 6 to 12 years. There is no unexpected accumulation at steady state in children.

Food does not affect the extent of absorption of d-amphetamine and l-amphetamine, but prolongs T_{max} by 2.5 hours (from 5.2 hrs at fasted state to 7.7 hrs after a high-fat meal) for d-amphetamine and 2.1 hours (from 5.6 hrs at fasted state to 7.7 hrs after a high fat meal) for l-amphetamine after administration of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules 30 mg. Opening the capsule and sprinkling the contents on applesauce results in comparable absorption to the intact capsule taken in the fasted state. Equal doses of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules strengths are bioequivalent.

Metabolism and Excretion

Amphetamine is reported to be oxidized at the 4 position of the benzene ring to form 4-hydroxyamphetamine, or on the side chain α or β carbons to form alpha-hydroxy-amphetamine or norephedrine, respectively. Norephedrine and 4-hydroxy-amphetamine are both active and each is subsequently oxidized to form 4-hydroxy-norephedrine. Alpha-hydroxy-amphetamine undergoes deamination to form phenylacetone, which ultimately forms benzoic acid and its glucuronide and the glycine conjugate hippuric acid. Although the enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with formation of 4-hydroxy-amphetamine. Since CYP2D6 is genetically polymorphic, population variations in amphetamine metabolism are a possibility.

Amphetamine is known to inhibit monoamine oxidase, whereas the ability of amphetamine and its metabolites to inhibit various P450 isozymes and other enzymes has not been adequately elucidated. *In vitro* experiments with human microsomes indicate minor inhibition of CYP2D6 by amphetamine and minor inhibition of CYP1A2, 2D6, and 3A4 by one or more metabolites. However, due to the probability of auto-inhibition and the lack of information on the concentration of these metabolites relative to *in vivo* concentrations, no predications regarding the potential for amphetamine or its metabolites to inhibit the metabolism of other drugs by CYP isozymes *in vivo* can be made.

With normal urine pHs approximately half of an administered dose of amphetamine is recoverable in urine as derivatives of alpha-hydroxy-amphetamine and approximately another 30%-40% of the dose is recoverable in urine as amphetamine itself. Since amphetamine has a pKa of 9.9, urinary recovery of amphetamine is highly dependent on pH and urine flow rates. Alkaline urine pHs result in less ionization and reduced renal elimination, and acidic pHs and high flow rates result in increased renal elimination with clearances greater than glomerular filtration rates, indicating the involvement of active secretion. Urinary recovery of amphetamine has been reported to range from 1% to 75%, depending on urinary pH, with the remaining fraction of the dose hepatically metabolized. Consequently, both hepatic and renal dysfunction have the potential to inhibit the elimination of amphetamine and result in prolonged exposures. In addition, drugs that effect urinary pH are known to alter the elimination of amphetamine, and any decrease in amphetamine's metabolism that might occur due to drug interactions or genetic polymorphisms is more likely to be clinically significant when renal elimination is decreased, (See PRECAUTIONS).

Special Populations

Comparison of the pharmacokinetics of d- and l-amphetamine after oral administration of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules in pediatric (6-12 years) and adolescent (13-17 years) ADHD patients and healthy adult volunteers indicates that body weight is the primary determinant of apparent differences in the pharmacokinetics of d- and l-amphetamine across the age range. Systemic exposure measured by area under the curve to infinity (AUC_∞) and maximum plasma concentration (C_{max}) decreased with increases in body weight, while oral volume of distribution (V_z/F), oral clearance (CL/F), and elimination half-life ($t_{1/2}$) increased with increases in body weight.

Pediatric Patients

On a mg/kg weight basis, children eliminated amphetamine faster than adults. The elimination half-life ($t_{1/2}$) is approximately 1 hour shorter for d-amphetamine and 2 hours shorter for l-amphetamine in children than in adults. However, children had higher systemic exposure to amphetamine (C_{max} and AUC) than adults for a given dose of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules, which was attributed to the higher dose administered to children on a mg/kg body weight basis compared to adults. Upon dose normalization on a mg/kg basis, children showed 30% less systemic exposure compared to adults.

Gender

Systemic exposure to amphetamine was 20-30% higher in women (N=20) than in men (N=20) due to the higher dose administered to women on a mg/kg body weight basis. When the exposure parameters (C_{max} and AUC) were normalized by dose (mg/kg), these differences diminished. Age and gender had no direct effect on the pharmacokinetics of d- and l-amphetamine.

Race

Formal pharmacokinetic studies for race have not been conducted. However, amphetamine pharmacokinetics appeared to be comparable among Caucasians (N=33), Blacks (N=8) and Hispanics (N=10).

CLINICAL TRIALS

Children

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in children aged 6-12 (N=584) who met DSM-IV® criteria for ADHD (either the combined type or the hyperactive-impulsive type). Patients were randomized to fixed dose treatment groups receiving final doses of 10, 20, or 30 mg of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules or placebo once daily in the morning for three weeks. Significant improvements in patient behavior, based upon teacher ratings of attention and hyperactivity, were observed for all Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules doses compared to patients who received placebo, for all three weeks, including the first week of treatment, when all Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules subjects were receiving a dose of 10 mg/day. Patients who received Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules showed behavioral improvements in both morning and afternoon assessments compared to patients on placebo.

In a classroom analogue study, patients (N=51) receiving fixed doses of 10 mg, 20 mg or 30 mg Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules demonstrated statistically significant improvements in teacher-rated behavior and performance measures, compared to patients treated with placebo.

Adolescents

A double-blind, randomized, multi-center, parallel-group, placebo-controlled study was conducted in adolescents aged 13-17 (N=327) who met DSM-IV® criteria for ADHD. The primary cohort of patients (n=287, weighing ≤ 75kg/165lbs) was randomized to fixed dose treatment groups and received four weeks of treatment. Patients were randomized to receive final doses of 10 mg, 20 mg, 30 mg, and 40 mg Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules or placebo once daily in the morning; patients randomized to doses greater than 10 mg were titrated to their final doses by 10 mg each week. The secondary cohort consisted of 40 subjects weighing >75kg/165lbs who were randomized to fixed dose treatment groups receiving final doses of 50 mg and 60 mg Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules or placebo once daily in the morning for 4 weeks. The primary efficacy variable was the ADHD-RS-IV total scores for the primary cohort. Improvements in the primary cohort were statistically significantly greater in all four primary cohort active treatment groups (Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules 10 mg, 20 mg, 30 mg, and 40 mg) compared with the placebo group. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

Adults

A double-blind, randomized, placebo-controlled, parallel-group study was conducted in adults (N=255) who met DSM-IV® criteria for ADHD. Patients were randomized to fixed dose treatment groups receiving final doses of 20, 40, or 60 mg of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules or placebo once daily in the morning for four weeks. Significant improvements, measured with the Attention Deficit Hyperactivity Disorder-Rating Scale (ADHD-RS), an 18- item scale that measures the core symptoms of ADHD, were observed at endpoint for all Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules doses compared to patients who received placebo for all four weeks. There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

INDICATIONS

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).
The efficacy of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, one controlled trial in adolescents aged 13 to 17, and one controlled trial in adults who met DSM-IV® criteria for ADHD (see CLINICAL PHARMACOLOGY), along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance.

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV®) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV® characteristics.

Need for Comprehensive Treatment Program

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Long-Term Use

The effectiveness of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules for long-term use, i.e., for more than 3 weeks in children and 4 weeks in adolescents and adults, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.
Agitated states.
Patients with a history of drug abuse.
During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Serious Cardiovascular Events

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug (see CONTRAINDICATIONS).

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs (see CONTRAINDICATIONS).

Hypertension and other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm) [see ADVERSE EVENTS], and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia (see CONTRAINDICATIONS).

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g. electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events

Pre-Existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible induction of mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence

that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth
Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was –1.1 lbs. and –2.8 lbs., respectively, for patients receiving 10 mg and 20 mg Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth, however, it is anticipated that they will likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

Seizures
There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in the absence of seizures, and very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance
Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

PRECAUTIONS

General
The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules should be used with caution in patients who use other sympathomimetic drugs.

Tics
Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's Syndrome in children and their families should precede use of stimulant medications.

Information for Patients
Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.
Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with amphetamine and should counsel them in its appropriate use. A patient Medication Guide is available for Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Drug Interactions
Acidifying agents

Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) lower absorption of amphetamines.

Urinary acidifying agents

These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

Adrenergic blockers

Adrenergic blockers are inhibited by amphetamines.

Alkalinizing agents

Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Co-administration of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.

Proton Pump Inhibitors

act on proton pumps by blocking acid production thereby reducing gastric acidity. In the presence of a proton pump inhibitor, the median T_{max} of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules was shortened from 5 hours to 2.75 hours. Therefore, co-administration of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules and proton pump inhibitors should be avoided.

Antidepressants, tricyclic

Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO inhibitors

MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines

Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives

Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine

Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.

Ethosuximide

Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol

Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.

Lithium carbonate

The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meperidine

Amphetamines potentiate the analgesic effect of meperidine.

Methenamine therapy

Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.

Norepinephrine

Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital

Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin

Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene

In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum alkaloids

Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions
Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis and Impairment of Fertility
No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m ^{2} body surface area basis.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m^2 body surface area basis).

Pregnancy

Pregnancy Category C

Amphetamine, in the enantiomer ratio present in ADDERALL® (d- to l- ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m^2 body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times that of a human dose of 30 mg/day [child] on a mg/m^2 basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Usage in Nursing Mothers
Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use
Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules is indicated for use in children 6 years of age and older.

Use in Children Under Six Years of Age
Effects of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules in 3-5 year olds have not been studied. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age.

Geriatric Use
Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules has not been studied in the geriatric population.

ADVERSE EVENTS

Hypertension
[See WARNINGS section] In a controlled 4-week outpatient clinical study of adolescents with ADHD, isolated systolic blood pressure elevations ≥15 mmHg were observed in 7/64 (11%) placebo-treated patients and 7/100 (7%) patients receiving Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules 10 or 20 mg. Isolated elevations in diastolic blood pressure ≥ 8 mmHg were observed in 16/64 (25%) placebo-treated patients and 22/100 (22%) Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules -treated patients. Similar results were observed at higher doses.
In a single-dose pharmacokinetic study in 23 adolescents, isolated increases in systolic blood pressure (above the upper 95% CI for age, gender, and stature) were observed in 2/17 (12%) and 8/23 (35%), subjects administered 10 mg and 20 mg Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules, respectively. Higher single doses were associated with a greater increase in systolic blood pressure. All increases were transient, appeared maximal at 2 to 4 hours post dose and not associated with symptoms.
The premarketing development program for Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules included exposures in a total of 1315 participants in clinical trials (635 pediatric patients, 350 adolescent patients, 248 adult patients, and 82 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N= 40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.
Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events.
The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

Adverse events associated with discontinuation of treatment
In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules in controlled and uncontrolled, multiple-dose clinical trials of pediatric patients (N=595) are presented below. Over half of these patients were exposed to Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules for 12 months or more.

Adverse event	% of pediatric patients discontinuing (n=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight loss	1.2

Emotional lability	1.0
Depression	0.7

In a separate placebo-controlled 4-week study in adolescents with ADHD, eight patients (3.4%) discontinued treatment due to adverse events among Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules -treated patients (N=233). Three patients discontinued due to insomnia and one patient each for depression, motor tics, headaches, light-headedness, and anxiety.
In one placebo-controlled 4-week study among adults with ADHD, patients who discontinued treatment due to adverse events among Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules -treated patients (N=191) were 3.1% (n=6) for nervousness including anxiety and irritability, 2.6% (n=5) for insomnia, 1% (n=2) each for headache, palpitation, and somnolence; and, 0.5% (n=1) each for ALT increase, agitation, chest pain, cocaine craving, elevated blood pressure, and weight loss.

Adverse events occurring in a controlled trial
Adverse events reported in a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adolescents and adults, respectively, treated with Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules or placebo are presented in the tables below.
The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.
Table 1 Adverse Events Reported by More Than 1% of Pediatric Patients Receiving Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules with Higher Incidence Than on Placebo in a 584 Patient Clinical Study

Body System	**Preferred Term**	**MAS-ER (n=374)**	**Placebo (n=210)**
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Lability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	Weight Loss	4%	0%

Table 2 Adverse Events Reported by 5% or more of Adolescents Weighing ≤ 75 kg/165 lbs Receiving Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules with Higher Incidence Than Placebo in a 287 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	**Preferred Term**	**MAS-ER (n=233)**	**Placebo (n=54)**
General	Abdominal Pain (stomachache)	11%	2%
Digestive System	Loss of Appetite †	36%	2%
Nervous System	Insomnia † Nervousness	12% 6%	4% 6%‡

Metabolic/Nutritional	Weight Loss †	9%	0%

Note: The following events did not meet the criterion for inclusion in Table 2 but were reported by 2% to 4% of adolescent patients receiving Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules with a higher incidence than patients receiving placebo in this study: accidental injury, asthenia (fatigue), dry mouth, dyspepsia, emotional lability, nausea, somnolence, and vomiting.

*****Included doses up to 40 mg

†Dose-related adverse events

‡Appears the same due to rounding

Table 3 Adverse Events Reported by 5% or More of Adults Receiving Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules with Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	**Preferred Term**	**MAS-ER (n=191)**	**Placebo (n=64)**
General	Asthenia	6%	5%
	Headache	26%	13%
Digestive System	Loss of Appetite	33%	3%
	Diarrhea	6%	0%
	Dry Mouth	35%	5%
	Nausea	8%	3%
Nervous System	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Insomnia	27%	13%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%
Urogenital System	Urinary Tract Infection	5%	0%

Note: The following events did not meet the criterion for inclusion in Table 3 but were reported by 2% to 4% of adult patients receiving Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder, emotional lability, libido decreased, somnolence, speech disorder, palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.

*****Included doses up to 60 mg.

The following adverse reactions have been associated with the use of amphetamine, Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules, or ADDERALL®:

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects.

Allergic: Urticaria, rash, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules is a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to levels many times higher than recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

OVERDOSAGE

Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Symptoms

Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment

Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

The prolonged release of mixed amphetamine salts from Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules should be considered when treating patients with overdose.

DOSAGE AND ADMINISTRATION

Dosage should be individualized according to the therapeutic needs and response of the patient. Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules should be administered at the lowest effective dosage.

Children

In children with ADHD who are 6 years of age and older and are either starting treatment for the first time or switching from another medication, start with 10 mg once daily in the morning; daily dosage may be adjusted in increments of 5 mg or 10 mg at weekly intervals. When in the judgment of the clinician a lower initial dose is appropriate, patients may begin treatment with 5 mg once daily in the morning. The maximum recommended dose for children is 30 mg/day; doses greater than 30 mg/day of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsuleshave not been studied in children. Amphetamines are not recommended for children under 3 years of age. Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules has not been studied in children under 6 years of age.

Adolescents

The recommended starting dose for adolescents who are 13-17 years of age with ADHD is 10 mg/day. The dose may be increased to 20 mg/day after one week if ADHD symptoms are not adequately controlled.

Adults

In adults with ADHD who are either starting treatment for the first time or switching from another medication, the recommended dose is 20 mg/day.

Patients Currently Using ADDERALL® - Based on bioequivalence data, patients taking divided doses of immediate-release ADDERALL®, for example twice a day, may be switched to Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules at the same total daily dose taken once daily. Titrate at weekly intervals to appropriate efficacy and tolerability as indicated.

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce. If the patient is using the sprinkle administration method, the sprinkled applesauce should be consumed immediately; it should not be stored. Patients should take the applesauce with sprinkled beads in its entirety without chewing. The dose of a single capsule should not be divided. The contents of the entire capsule should be taken, and patients should not take anything less than one capsule per day.

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules may be taken with or without food.

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules should be given upon awakening. Afternoon doses should be avoided because of the potential for insomnia.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy**.**

HOW SUPPLIED

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release (MAS-ER) Capsules are available as:

5 mg- Clear/blue (imprinted M. Amphet Salts 5 mg), bottles of 100, NDC 0115-1328-01
10 mg- Blue/blue (imprinted M. Amphet Salts 10 mg), bottles of 100, NDC 0115-1329-01
15 mg- Blue/white (imprinted M. Amphet Salts 15 mg), bottles of 100, NDC 0015-1330-01
20 mg- Orange/orange (imprinted M. Amphet Salts 20 mg), bottles of 100, NDC 0115-1331-01
25 mg- Orange/white (imprinted M. Amphet Salts 25 mg), bottles of 100, NDC 0115-1332-01
30 mg- Natural/orange (imprinted M. Amphet Salts 30 mg), bottles of 100, NDC 0115-1333-01

Dispense in a tight, light-resistant container as defined in the USP.
Store at 25º C (77º F). Excursions permitted to 15-30º C (59-86º F) [see USP Controlled Room Temperature]

ANIMAL TOXICOLOGY

Acute administration of high doses of amphetamine (d- or d,l-) has been shown to produce long-lasting neurotoxic effects, including irreversible nerve fiber damage, in rodents. The significance of these findings to humans is unknown.

Manufactured for Global Pharmaceuticals, Division of IMPAX Laboratories, Inc.,
Philadelphia, PA 19124 USA
Supplied by Shire LLC, Florence, KY 41042
Made in USA
For more information contact IMPAX Laboratories, Inc., at
1-800-934-6729

Pharmacist: Medication Guide to be dispensed to patients

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Rev.10/09

MEDICATION GUIDE

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules (mixed salts of a single- entity amphetmanine product)

Read the Medication Guide that comes with Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules before you or your child starts taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about you or your child's treatment with Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules.

What is the most important information I should know about Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules?

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules is a stimulant medicine. The following have been reported with use of stimulant medicines.

1. Heart-related problems:

- **sudden death in patients who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules.

Your doctor should check you or your child's blood pressure and heart rate regularly during treatment with Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules.

2. Mental (Psychiatric) problems:

All Patients

- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new or worse aggressive behavior or hostility**

Children and Teenagers

- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

Tell your doctor about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

What Is Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules?

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules is a once daily central nervous system stimulan**t** prescription medicine. **It is used for the treatment of Attention Deficit Hyperactivity Disorder(ADHD).** Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules in a safe place to prevent misuse and abuse. Selling or giving away Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules may harm others, and is against the law.

Tell your doctor if you or your child have (or have a family history of) ever abused or been dependent on alcohol, prescription medicines or street drugs.

Who should not take Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules?

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules should not be taken if you or your child:

- have heart disease or hardening of the arteries
- have moderate to severe high blood pressure
- have hyperthyroidism
- have an eye problem called glaucoma

- are very anxious, tense, or agitated
- have a history of drug abuse
- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.
- is sensitive to, allergic to, or had a reaction to other stimulant medicines

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules has not been studied in children less than 6 years old.
Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules is not recommended for use in children less than 3 years old.
Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules may not be right for you or your child. Before starting Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules tell your or your child's doctor about all health conditions (or a family history of) including:
- heart problems, heart defects, or high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- tics or Tourette's syndrome
- liver or kidney problems
- thyroid problems
- seizures or have had an abnormal brain wave test (EEG)

Tell your doctor if you or your child is pregnant, planning to become pregnant, or breastfeeding.
Can Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules be taken with other medicines?
Tell your doctor about all of the medicines that you or your child takes including prescription and non-prescription medicines, vitamins, and herbal supplements. Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules.
Your doctor will decide whether Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules can be taken with other medicines.
Especially tell your doctor if you or your child takes:
- anti-depression medicines including MAOIs
- anti-psychotic medicines
- lithium
- narcotic pain medicines
- seizure medicines
- blood thinner medicines
- blood pressure medicines
- stomach acid medicines
- cold or allergy medicines that contain decongestants

Know the medicines that you or your child takes. Keep a list of your medicines with you to show your doctor and pharmacist.
Do not start any new medicine while taking Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules without talking to your doctor first.
How should Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules be taken?

- **Take Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules exactly as prescribed.** Your doctor may adjust the dose until it is right for you or your child.

- Take Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules once a day in the morning when you first wake up Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules is an extended release capsule. It releases medicine into your body throughout the day.

- Swallow Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules capsules whole with water or other liquids. If you or your child cannot swallow the capsule, open it and sprinkle the medicine over a spoonful of applesauce. Swallow all of the applesauce and medicine mixture without chewing immediately. Follow with a drink of water or other liquid. **Never chew or crush the capsule or the medicine inside the capsule.**

- Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules can be taken with or without food.

- From time to time, your doctor may stop Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules treatment for a while to check ADHD symptoms.

- Your doctor may do regular checks of the blood, heart, and blood pressure while taking Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules. Children should have their height and weight checked often while taking Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules. Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules treatment may be stopped if a problem is found during these check-ups.

- **If you or your child takes too much Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules or overdoses, call your doctor or poison control center right away, or get emergency treatment.**

What are possible side effects of Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules?
See **"What is the most important information I should know about Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules?"** for information on reported heart and mental problems.
Other serious side effects include:
- slowing of growth (height and weight) in children

- seizures, mainly in patients with a history of seizures

- eyesight changes or blurred vision

Common side effects include:
- headache

- decreased appetite

- stomach ache

- nervousness

- trouble sleeping

- mood swings

- weight loss

- dizziness

- dry mouth

• fast heart beat

Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules may affect you or your child's ability to drive or do other dangerous activities.
Talk to your doctor if you or your child has side effects that are bothersome or do not go away.
This is not a complete list of possible side effects. Ask your doctor or pharmacist for more information
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules?

- Store Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules in a safe place at room temperature, 59 to 86° F (15 to 30° C).

- **Keep Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules and all medicines out of the reach of children.**

General information about Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules for a condition for which it was not prescribed. Do not give Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules to other people, even if they have the same condition. It may harm them and it is against the law.
This Medication Guide summarizes the most important information about Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules that was written for healthcare professionals. For more information, you may also contact IMPAX Laboratories Inc., at 1-800-934-6729.

What are the ingredients in Dextroamphetamine Saccharate, Amphetamine Asparate Monohydrate, Dextroamphetamine Sulfate and, Amphetamine Sulfate Extended-Release Capsules?

Active Ingredients: dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, USP, amphetamine sulfate USP

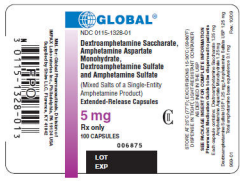
Inactive Ingredients: gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, opadry beige, sugar spheres, talc, and triethyl citrate. Gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 5 mg, 10 mg, and 15 mg capsules also contain FD&C Blue #2. The 20 mg, 25 mg, and 30 mg capsules also contain red iron oxide and yellow iron oxide

Manufactured for Global Pharmaceuticals, Division of IMPAX Laboratories, Inc., Philadelphia, PA 19124 USA
Supplied by Shire LLC, Florence, KY 41042
Rev. 10/09
974-01 108964

This Medication Guide has been approved by the U.S. Food and Drug Administration.

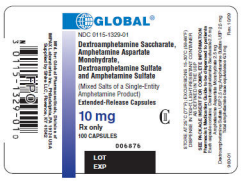
PRINCIPAL DISPLAY PANEL - 5 MG LABEL

GLOBAL®
NDC 0115-1328-01
Dextroamphetamine Saccharate,
Amphetamine Aspartate
Monohydrate,
Dextroamphetamine Sulfate
and Amphetamine Sulfate
(Mixed Salts of a Single-Entity
Amphetamine Product)
Extended-Release Capsules
CII
5 mg
Rx only
100 CAPSULES
006875
LOT
EXP



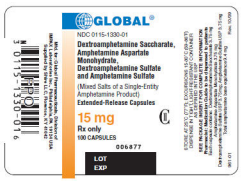
PRINCIPAL DISPLAY PANEL - 10 MG LABEL

GLOBAL®
NDC 0115-1329-01
Dextroamphetamine Saccharate,
Amphetamine Aspartate
Monohydrate,
Dextroamphetamine Sulfate
and Amphetamine Sulfate
(Mixed Salts of a Single-Entity
Amphetamine Product)
Extended-Release Capsules
CII
10 mg
Rx only
100 CAPSULES
006876
LOT
EXP



PRINCIPAL DISPLAY PANEL - 15 MG LABEL

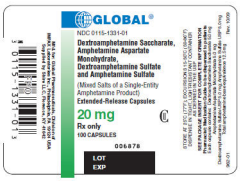
GLOBAL®
NDC 0115-1330-01
Dextroamphetamine Saccharate,
Amphetamine Aspartate
Monohydrate,
Dextroamphetamine Sulfate
and Amphetamine Sulfate
(Mixed Salts of a Single-Entity
Amphetamine Product)
Extended-Release Capsules
CII
15 mg
Rx only
100 CAPSULES
006877
LOT
EXP



PRINCIPAL DISPLAY PANEL - 20 MG LABEL

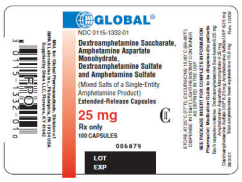
GLOBAL®

NDC 0115-1331-01
Dextroamphetamine Saccharate,
Amphetamine Aspartate
Monohydrate,
Dextroamphetamine Sulfate
and Amphetamine Sulfate
(Mixed Salts of a Single-Entity
Amphetamine Product)
Extended-Release Capsules
CII
20 mg
Rx only
100 CAPSULES
006878
LOT
EXP



PRINCIPAL DISPLAY PANEL - 25 MG LABEL

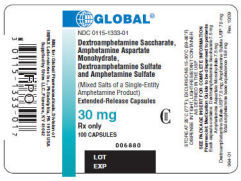
GLOBAL®
NDC 0115-1332-01
Dextroamphetamine Saccharate,
Amphetamine Aspartate
Monohydrate,
Dextroamphetamine Sulfate
and Amphetamine Sulfate
(Mixed Salts of a Single-Entity
Amphetamine Product)
Extended-Release Capsules
CII
25 mg
Rx only
100 CAPSULES
006879
LOT
EXP



PRINCIPAL DISPLAY PANEL - 30 MG LABEL

GLOBAL®
NDC 0115-1333-01
Dextroamphetamine Saccharate,
Amphetamine Aspartate
Monohydrate,
Dextroamphetamine Sulfate
and Amphetamine Sulfate
(Mixed Salts of a Single-Entity
Amphetamine Product)
Extended-Release Capsules

CII
30 mg
Rx only
100 CAPSULES
006880
LOT
EXP



Revised: 12/2009

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